A Case of Idiopathic Systemic Capillary Leak Syndrome with High Serum Levels of G-CSF on Exacerbation

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Abstract

Systemic capillary leak syndrome (SCLS) is a life-threatening disorder which presents with periodic episodes of hypovolemic shock, due to plasma leakage to the extra-vascular space reflected by accompanying hypoalbuminemia, hemoconcentration and edema often with associated monoclonal gammapathy. We describe a 28-year-old woman with SCLS who required aggressive fluid resuscitation and was successfully treated with corticosteroid, terbutaline, and theophylline. At exacerbation, the levels of serum granulocyte colony-stimulating factor (G-CSF) were increased. Thus, G-CSF might play an important role and can be a useful biomarker for the severity of attacks in SCLS.

Key words: systemic capillary leak syndrome, granulocyte colony-stimulating factor


Introduction

Systemic capillary leak syndrome (SCLS) is a very rare idiopathic disorder which presents with periodic episode of hypovolemic shock, due to plasma leakage to the extra-vascular space reflected by accompanying hypoalbuminemia, hemoconcentration and edema, and in most cases, the presence of a paraproteinemia (1, 2). Clinical signs during attacks result from extravasation of large volumes of plasma from the intravascular space to the interstitial space. The secondary development of compartment syndrome or rhabdomyolysis from the swelling of muscle compartments is a rare complication. Clarkson described the first case of SCLS in 1960 (1), and about 150 patients have been described since (2-6). The frequency of reports has increased in the past decade, probably due to an increased clinical awareness of the syndrome, however the true incidence of SCLS may be underestimated. Clinicians need to be aware that this syndrome has an underlying diagnostic difficulty and carries a high mortality. Thus, it is hoped to discover a new molecule to monitor this syndrome. We present a patient with SCLS who was treated successfully with corticosteroid, beta-2 agonists and theophylline and found a relationship between serum levels of granulocyte colony-stimulating factor and the severity of attacks in SCLS.

Case Report

A 28-year-old woman was admitted to our hospital with generalized edema and circulatory shock in July 2006. She had previously been hospitalized three times at another hospital over the past 6 months with oliguria, hypotension and generalized edema. She presented at the emergency room with oliguria and a feeling of dizziness and fatigue. On examination her systolic blood pressure was 82 mmHg, pulse
rate 150/min and body temperature 35.0°C. Her neck veins had collapsed and there was generalized edema which was pitting on the legs. Respiratory examination revealed dullness on percussion and decreased breath sounds at lung bases. Cardiovascular and abdominal examination showed no particular abnormality. Chest X-ray confirmed bilateral pleural effusions (Fig. 1a). Electrocardiogram and echocardiogram were normal. Hemoglobin was 22.8 g/dL, hematocrit 64.1%, total leukocyte count 20,450/μL, platelet count 221,000/μL, blood urea nitrogen 31 mg/dL, serum creatinine 1.67 mg/dL, serum sodium 138 mEq/L, serum potassium 5.2 mEq/L, total serum protein 5.7 g/dL, serum albumin 3.0 g/dL and ALT/AST 48/10 IU/L. IgG, IgA and IgM were 845.1 mg/dL, 98.0 mg/dL and 112.0 mg/dL, respectively. Plasma level of lactate was 15.0 mg/dL, pyruvate 0.6 mg/dL and CPK 68 IU/L. Arterial blood gas analysis showed the following values: pH 7.26, PaO2 53 mmHg, PaCO2 45 mmHg and HCO3⁻ 19.6 mEq/L. She was diagnosed with severe erythrocytosis and therefore initially referred to a hematologist. She was admitted and received 6 liters of intravenous fluid in 24 hours (a mixture of normal saline, crystalloid and colloid solutions) to maintain a systolic BP of 90 mmHg and high flow oxygen 7 L/min to maintain SpO2 more than 90%. She only passed 30 mL of urine on the first day. On the second day, she continued to require inotropic support and oxygen to maintain her systolic blood pressure above 90 mmHg and oxygen saturation, but her urine output improved to 600 mL and her oxygen requirement decreased to 3 L/min. Her urine examination revealed trace protein and no active sediment. Hemoglobin fell to 11.0 g/dL but there was no evidence of any bleeding. On the third day her urine output rose further to 2 L/day and she was taken off oxygen and inotropes. Chest X-ray showed no pleural effusion (Fig. 1b), suggesting that massive fluid recruitment from tissues into circulation and massive diuresis occurs because capillary barrier function has been restored.

To establish a diagnosis, the patient was transferred to our division of internal medicine. Extensive testing for possible causes was carried out. No infectious cause was found in any of these episodes. Furthermore, there was never any fever or documented focus. A computed tomography of the chest and abdomen, and cardiac functional tests revealed no abnormalities after the attack. Monoclonal immunoglobulin G-lambda was detected in the patient’s serum by immunoelectrophoresis, but Bence Jones protein was negative. A bone marrow aspiration showed no abnormality. Notably, the level of G-CSF had increased to 57 pg/mL (normal: <39 pg/mL). Other laboratory investigations, including interleukin-2 (IL-2) (0.7 U/mL, normal: <0.8 U/mL), interleukin-6 (IL-6) (1.4 pg/mL, normal: <4.0 pg/mL), vascular endothelial growth factor (VEGF) (<31 pg/mL, normal: <38 pg/mL), autoantibodies, complement studies, and Cl esterase inhibitor measurement, were all normal on admission. This young woman had experienced three episodes of unexplained shock in the previous 6 months, accompanied by evidence of capillary leakage in the form of generalized edema and bilateral pleural effusion, and was thus diagnosed with idiopathic systemic capillary leak syndrome by the presence of the characteristic triad of hypotension, hemoconcentration and hypoalbuminemia with monoclonal gammopathy. She was started on prophylactic treatment with beta-2 agonists and theophylline in combination with steroid therapy (prednisolone, 30 mg/day) because it was reported that macromolecule leakage in response to various stimuli, including

**Figure 1.** Chest X-ray taken on admission, showing bilateral pulmonary infiltrates and pleural effusions (A). Chest X-ray taken on day 3, showing no pleural effusion (B).
histamine and bradykinin, can be inhibited by pretreatment with beta-2 agonists, theophylline and steroid therapy (2-4).

While tapering prednisolone, she was re-admitted in October 2006 and November 2008 with similar episodes of self-limiting shock, which were resolved within 4 to 6 days with supportive therapy in the form of intravenous fluids and inotropes. Again investigations failed to reveal any cause. Interestingly, the levels of serum G-CSF had increased (maximum, 279 pg/mL) on admission and were significantly associated with the levels of blood neutrophils (r=0.730, p<0.0001) (Fig. 2). After administration of prednisolone, G-CSF levels showed a gradual decrease that coincided with improvement in the clinical course. Therefore, we used serum G-CSF levels as a marker of disease activity. Although she had chronic treatment with prednisolone ranging from 10 mg/day to 20 mg/day, she had self-limiting attacks, which were resolved within 3 days by drinking mineral water.

**Discussion**

To our knowledge, this is the first report in which G-CSF levels showed a relationship with the disease activity of SCLS attacks. Although the underlying pathophysiology is unknown, the presence of a monoclonal paraprotein is considered a characteristic manifestation of SCLS. In a review of the literature published in 2002 (4), 47 of 56 patients with SCLS had a monoclonal protein, predominantly IgG-kappa. The cumulative probability of progression of monoclonal gammopathy to myeloma or related plasma cell disorder has been reported as 10% at ten years, 21% at 20 years, and 26% at 25 years following diagnosis (7). There had been no reports of familial cases, until recently, a case of familial SCLS was reported (8). Despite many reports proposing mechanisms involving disparate biochemical substances or cells which might act on the capillaries to cause their leaking, no consistent mechanism has been proven (4-6). Serum levels of complements, kinins, prostaglandin, coagulation factors, histamine and serotonin are usually normal in patients with SCLS. Activation of the 5-lipoxygenase pathway and a role for IL-2, VEGF and interferon-β has been suggested (9-12). It has also been reported that SCLS occurs after infusions of IL-2, IL-4, tumor necrosis factor, granulocyte-macrophage colony-stimulating factor (GM-CSF) and granulocyte colony-stimulating factor (G-CSF) as well as after autologous and allogeneic stem cell transplantation (13-15).

In the present patient, serum G-CSF levels, but not IL-2, IL-6 and VEGF levels, increased parallel to disease activity and were significantly associated with the levels of blood neutrophils. Recombinant human G-CSF increases neutrophil count and enhances their phagocytic and cytotoxic functions as well as their expression of adhesion molecules (16). Dagdemir et al reported that a patient developed SCLS twice while receiving G-CSF, without any time relationship between the onset of symptoms and the rapid increase in white blood cell count (17). They suggested that a direct effect of G-CSF on the endothelium may have played
a major role and that G-CSF is able to cause SCLS even when the white blood cell count is very low. Based on these reports, G-CSF might have triggered neutrophil activation and the release of inflammatory mediators, resulting in tissue damage and systemic manifestations of increased capillary permeability in the present patient. It remains unknown what triggers and what kind of cells could release G-CSF during SCLS exacerbations. Bone marrow plasma cells might have the potential for release G-CSF because a monoclonal paraprotein presents in most patients with SCLS. We did not find a significant relationship between prodromal symptoms, such as flu-like symptoms and increases of serum G-CSF. Therefore, further investigation is needed to clarify the relationship between G-CSF and SCLS.

Treatment of SCLS with corticosteroids may be beneficial, since it interferes with granulocyte function and cytokine release (18). In fact, administration of prednisolone was effective in decreasing G-CSF levels with improvement in the clinical course in the present case. Furthermore, compounds that prevent cyclic adenosine monophosphate degradation and increase intracellular cyclic adenosine monophosphate levels, such as beta-adrenergic agonists and phosphodiesterase inhibitors (theophylline), have been used and are effective in many patients with SCLS (2-6). We therefore used beta-2 agonists and theophylline for prophylactic treatment. In the present case, serum G-CSF levels were elevated before the treatment with prednisolone, theophylline, and terbutaline and showed a relationship with the clinical course; however, SCLS might not be due to a single pathogenesis. Nagao et al reported that 18 cytokines were measured and G-CSF, IL-6, IL-8 and MCP-1 were significantly elevated (19), but we did not measure IL-8 and MCP-1. Therefore, in some SCLS, G-CSF might be useful, but not all cases. In the future, it is hoped that this avenue of research will clarify the pathophysiology and the treatment of SCLS.

In conclusion, although the pathophysiology of SCLS is unknown, we present a patient with SCLS who was treated successfully with corticosteroid, beta-2 agonists and theophylline and we found a relationship between the serum levels of granulocyte colony-stimulating factor and the clinical course. Thus, G-CSF might play an important role and can be a useful biomarker for the severity of attacks in SCLS.

The authors state that they have no Conflict of Interest (COI).

References


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